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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,854	06/21/2001	Krys Bankiewicz	0800-0014.01	9216

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,854	BANKIEWICZ ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004 and 18 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22 and 25-27* is/are rejected.

7)☒ Claim(s) *23 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-18-04 has been entered.

Applicants' amendment filed 4-19-04 has been entered. Claim 21 has been amended. Claims 26 and 27 have been added. Claims 21-27 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "over an area of at least 40-50 mm^2" in claims 26 and 27 is considered new matter. The amendment filed 4-19-04 indicates the support for the phrase "over the area of at least 40-50 mm^2" is shown in Figures 1B and 3B of the specification. However, Figures 1B and 3B only show specific point value of mean area, for example, about 49 mm^2 for IP and about 45

mm^2 for OP in Figure 3B, and about 50 mm^2 in Figure 1B. Figures 1B and 3B fail to provide support for a specific range of mean area, such as 40-50 mm^2. Thus, the phrase "over an area of at least 40-50 mm^2" in claims 26 and 27 is considered new matter.

4. Claims 21, 22 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering recombinant adeno-associated virus (rAAV) expressing a protein to monkey brain by intrastriatal administration of said rAAV via the use of infusion pump or osmotic pump such that distribution of said rAAV virus is over an area greater than 5 mm^2, does not reasonably provide enablement for a method of delivering a pharmaceutical composition comprising a rAAV expressing a protein to the brain of a subject having central nervous system (CNS) disorder via any administration route or administration mean other than infusion pump or osmotic pump such that distribution of said rAAV virus is over an area greater than 5 mm^2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 21, 22 and 25 are directed to a method of delivering a pharmaceutical composition comprising a rAAV expressing a protein to the brain of a subject such that distribution of said rAAV virus is over an area greater than 5 mm^2. Claims 22 specifies the rAAV is delivered using convection enhanced delivery (CED). Claim 25 specifies the rAAV is administered to the striatum.

The specification only discloses delivery of rAAV virus to the striatum of a rats or a monkey by drilling a hole on the head with a dental drill and deliver the rAAV virus with either

infusion pump or osmotic pump via a needle (see Example 2 and 3). The claims encompass delivering the rAAV virus expressing a protein to the brain of a subject via any administration route or administration apparatus to the brain such that the rAAV virus is distributed in the brain over an area greater than 5 mm^2. The specification defines the "convection-enhanced delivery" as any non-manual delivery of agents (specification, page 14, line 27).

The specification fails to provide adequate guidance and evidence for how to deliver a rAAV virus expressing a protein to the brain of a subject via any administration route or administration apparatus to the brain other than infusion pump and osmotic pump such that the rAAV virus is distributed in the brain over an area greater than 5 mm^2. Claims 21 and 25 encompass manual administration of the rAAV virus to the brain of a subject, for example, manual injection of the rAAV virus. It was well known in the art that the distribution of a vector is usually limited to the needle tract of the injection site while the vector is delivered via needle injection. For example, the Passini reference (Methods in Molecular Biology, Ed. W.C. Hessler, Vol. 246, pp. 225-236) submitted by applicants in the amendment filed 4-19-04 states that "[a] feature of AAV2 transduction in the brain is that the vector remains confined to the injection site…" (e.g. p. 225). Further, as pointed out by applicants in the submitted Vite reference (Gene Therapy, 2003, Vol. 10, p. 1874-1881) in the amendment filed 4-19-04, administration of rAAV vector to the brain of a cat via needle injection can only achieve distribution to areas less than 5 mm^2 using approximately two orders of magnitude more vector than applicants use (see amendment, p. 7). It appears that it is not feasible to achieve distribution area greater than 5 mm^2 via manual injection of the rAAV vector into the brain of a target subject.

Claim 22 specifies the rAAV is delivered using convection enhanced delivery (CED), which is defined as any non-manual delivery of agents. A non-manual delivery of an agent broadly encompasses any delivery method that is not manual, such as using any mechanical method or pump other than osmotic pump and infusion pump, and electroporation etc. The specification fails to provide adequate guidance and evidence for how to deliver a rAAV virus expressing a protein to the brain of a subject via various non-manual delivery method, such as using any mechanical method or pump other than osmotic pump and infusion pump, and electroporation etc., such that the rAAV virus is distributed in the brain over an area greater than 5 mm^2. The specification fails to provide guidance for how much pump pressure, concentration of the rAAV vector and volume of the vector solution are required to achieve distribution area greater than 5 mm^2 in the brain. The specification also fails to provide adequate guidance for whether sufficient pressure, concentration of rAAV vector and volume of the vector solution can be provided by any non-manual delivery method other than infusion pump and osmotic pump such that distribution area greater than 5 mm^2 in the brain can be achieved. Further, the submitted Passini reference states that "intraventricular injection of AAV2 results in widespread brain transduction when the vector is administered into the cerebrospinal fluid (CSF) during neonatal development (32), whereas similar intraventricular injection into the adult brain results in very limited transduction pattern (7)." (e.g. bridging p. 226 and 227). It appears that the injection site and the developmental stage of the brain also play a role in the distribution efficiency of the administered rAAV vector in the brain. In addition, the cited Okada reference of record shows that stereotactically injected rAAV vector to the mouse brain with a 26 gauge needle using a microsyringe pump only results in distribution of the rAAV vector along the

needle tract (e.g. p. 963, right column, Figure 4). In view of the reasons set forth above, it is apparent that it was unpredictable at the time of the invention whether the administered rAAV vector would be distributed to an area greater than 5 mm^2 in the brain of a subject via various administration routes or apparatuses that is either manual injection or mechanic method or pump other than osmotic pump and infusion pump, or electroporation etc. Thus, one skilled in the art at the time of the invention would not know how to use the invention commensurate in scope with these claims.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

Claims 21, 22 and 25-27 are rejected. Claims 23 and 24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

S. Chen